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Absence of CD69 Expression on Peripheral Eosinophils in Episodic Angioedema and Eosinophilia

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A 45-year-old woman with episodic angioedema and eosinophilia is presented. CD69, which is one of the surface antigens of activated eosinophils, was not expressed on the peripheral eosinophils in this patient, in contrast to hypereosinophilic syndrome. This suggests that CD69, which is not dependent on eosinophil density, may be another useful activation marker of eosinophils to distinguish episodic angioedema and eosinophilia from hypereosinophilic syndrome. © 1996 Wiley-Liss, Inc.

Key words: episodic angioedema and eosinophilia, hypereosinophilic syndrome, CD69

INTRODUCTION

Episodic angioedema and eosinophilia is a recently proposed clinical entity which is distinct from hypereosinophilic syndrome (HES) [1,2]. Although peripheral marked hypereosinophilia is a common characteristic feature in these two syndromes, patients with episodic angioedema and eosinophilia have no involvement of critical organs and run a benign clinical course [1]. But until today, only a few differences have been demonstrated in the activation state of peripheral eosinophils between the two diseases [3]. In 1992, CD69 was proposed as a useful marker for evaluating the activation state of eosinophils [4]. We describe here a case of episodic angioedema and eosinophilia that did not express CD69 on peripheral eosinophils, in contrast to hypereosinophilic syndrome.

CASE REPORT

A 45-year-old woman was admitted to our hospital because of edema of the upper and lower limbs. She was well and had no allergic symptoms until May 1993, when she began to consume a healthy diet which contained L-arginine, L-lysine, L-ornithine, and cellulose, but not L-tryptophan, and she noticed a weight gain of 3 kg 5 days thereafter. But she continued to take this diet until June 10, when the total dosage was 122 tablets. At this point, she changed to a low-caloric diet, and 10 days after this therapy, she lost 4 kg. After stopping this regimen, her weight slowly increased and she noticed edema in the hands and lower limbs on July 10. She consulted our hospital on July 13, when marked leukocytosis with 57% of eosinophils was pointed out for the first time. Physical examination revealed lymph-node swelling of the right neck. Neither abnormal heart sounds nor friction rub was heard. There was nonpitting edema in the hands and lower extremities. White cell count was 23,000/mm^3 with 57% eosinophils. Hematocrit was 38.0%, and platelet count 348 $\times$ 10^9/l. Serum creatinine was 0.8 mg/dl, urea 11.2 mg/dl, uric acid 4.8 mg/dl, asparate aminotransferase 11 U/l, lactic dehydrogenase 480 U/l, and c-reactive protein 0.4 mg/dl. Serum IgG was 1,258 mg/dl, IgA 252 mg/dl, and IgM 249 mg/dl. IgE was not increased (17 IU/l). Complements were in the normal range (C3 73 mg/dl, normal, 55–115 mg/dl; C4 28 mg/dl, normal, 15–50 mg/dl; CH50 35 U/ml, normal, 30–40 μ/ml; C1-esterase inhibitor 17.5 mg/dl, normal, 15.0–35.0 mg/dl). Neither hepatomegaly nor splenomegaly was detected by abdominal ultrasonography. An electrocardiogram and chest X-ray findings revealed no evidence for cardiopulmonary involvement, which is usually found in hypereosinophilic syndrome. After admission, she lost 1.2 kg. A skin biopsy

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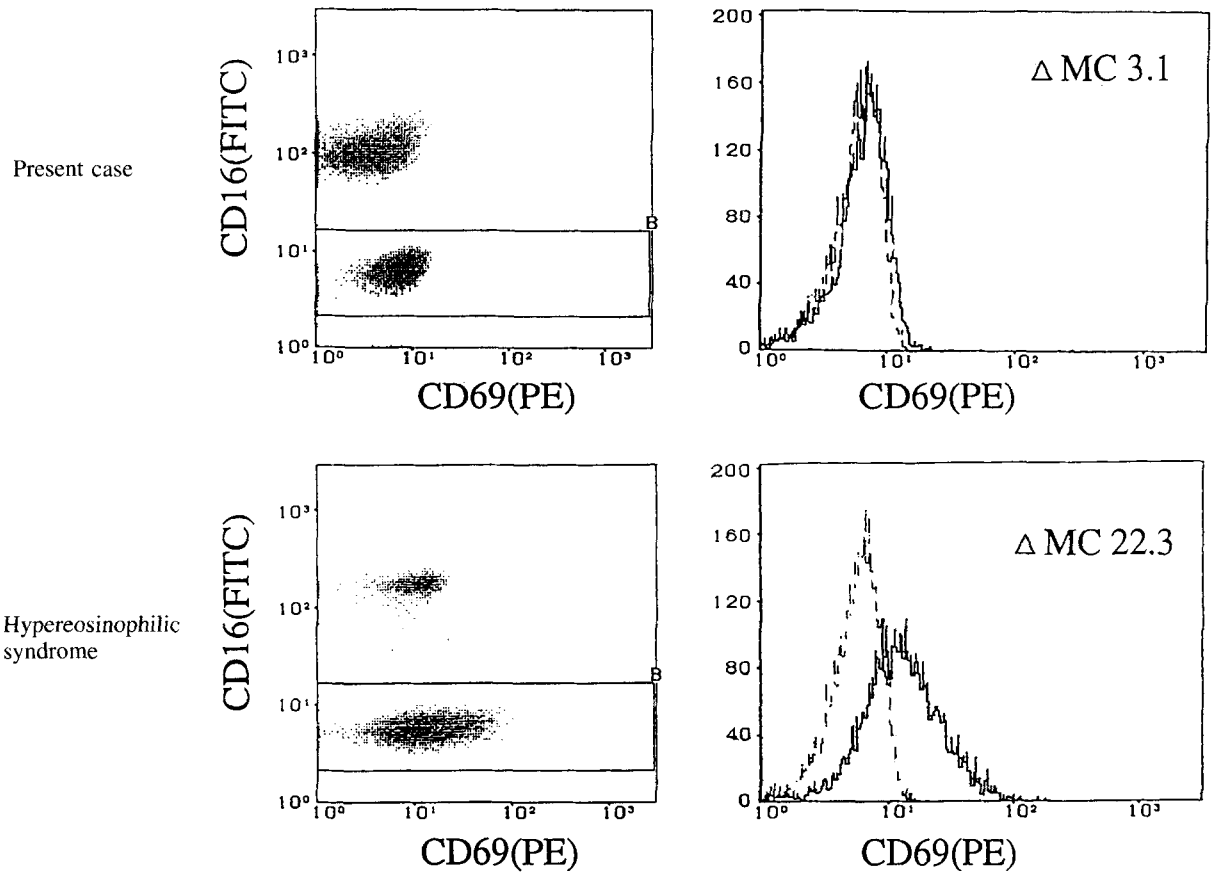

Fig. 1. Immunofluorescence analysis of CD69 expression on peripheral blood (PB) eosinophils. Comparison of fluorescence intensity of PE-conjugated anti-CD69 antibodies between our case and hypereosinophilic syndrome [5]. In polymorphonuclear leukocytes, the CD16-negative region was gated and analyzed with PE-conjugated anti-CD69 antibodies. Then, ΔMC of each patient was calculated (ΔMC means difference of mean fluorescence intensity between negative control staining, shown as dotted curves, and anti-CD69 antibodies staining, shown as solid curves).

specimen showed mild perivascular lymphocyte infiltration and eosinophilic infiltration, especially around the deep dermis capillary walls. Electron microscopic examination of peripheral blood eosinophils showed several granules undergoing degranulation, compatible with the findings reported by Gleich et al. [1]. On bone-marrow examination, 29.2% of total cells were eosinophils with normal maturation. Stool examination for ova or parasites and tests for antibodies against several parasites were all negative. Next, we examined surface markers of peripheral eosinophils, possibly indicative of an activation state of eosinophils, using monoclonal antibodies against CD69. In contrast to our pervious case of hypereosinophilic syndrome [5], CD69 was not expressed on peripheral eosinophils (Fig. 1). Based on these findings, episodic angioedema with eosinophilia was diagnosed, and corticosteroid therapy was started. The edema disappeared rapidly after administration of predonisone 20 mg/day. Five days after this therapy, white blood cell count decreased to 11,500/mm^3 with 5% eosinophils. But when the corticosteroid dose was decreased, the edema recurred, and so the dosage was increased.

DISCUSSION

In the present case, the findings of a skin biopsy specimen and electron microscopic examination of peripheral blood (PB) eosinophils suggested the pathogenetic involvement of eosinophils in angioedema. Triggers known to induce peripheral hypereosinophilia include several parasites, drugs, foods, and other allergens. A drug hypersensitivity reaction was ruled out because of the recurrence of edema without resumption of the slimming medicine. We did not find antibodies to a group of parasites which can induce hypereosinophilia. These findings and the clinical features of this case were consistent with episodic angioedema with eosinophilia, as previously reported by Gleich et al. [1], except for the normal serum levels of IgM. In addition, unlike that of Gleich et al. [1], our case did not have urticaria or fever. However, Take et al. [6] also reported four cases of episodic angioedema with eosinophilia, but elevated serum IgM and fever were not features in their cases. These facts suggest that episodic angioedema and eosinophilia, which was previously classified as a variant of HES, also has a wide clinical spectrum.

To differentiate this syndrome from HES is very important, because the prognosis and treatment are very different. As peripheral marked eosinophilia is a common feature of these two syndromes, one of the clues in identifying the pathophysiological difference between them involves differences in the activation state of PB eosinophils. One of the important parameters to evaluate the activation state of eosinophils is blood eosinophil density [7]. Lassalle et al. [3] demonstrated that the density of PB eosinophils in patients with HES is much lower than in patients with episodic angioedema and eosinophilia. They also detected the existence of anti-endothelial cell antibodies in sera of this syndrome, in contrast to patients with HES or normal controls [3]. But these parameters are difficult to evaluate on a routine basis.

CD69 is a surface antigen which is known to be expressed on activated T cells and natural killer cells [8]. Recently, it has been shown that CD69 is also expressed on activated lung eosinophils in eosinophilic pneumonia [4]. Although tissue-infiltrating eosinophils usually express CD69 antigen, hypodense PB eosinophils from mildly eosinophilic patients do not express CD69, and this molecule is induced on PB eosinophils after cytokine (IL-3, IL-5, or GM-CSF) stimulation [4]. This finding suggests that CD69 might be another useful activation marker of eosinophils which is independent of eosinophil density. Among these cytokines which can activate eosinophils, IL-3 and GM-CSF induce CD69 expression on eosinophils more strongly than IL-5 [4]. Hence, CD69 expression on PB eosinophils may strongly suggest the presence of systemic effect of IL-3 or GM-CSF. It is possible that eosinophils are activated and gain potent cytotoxic activity under the influence of these cytokines. This potent eosinophil activation might lead to systemic tissue injury in HES. In contrast, the absence of CD69 on PB eosinophils in our patient may be the characteristic feature of episodic angioedema and eosinophilia with benign clinical course. Recently, significant involvement of IL-5 but not IL-3 or GM-CSF in the pathogenesis of episodic angioedema and eosinophilia was demonstrated [9,10]. This fact may also explain why PB eosinophils from our patient did not express CD69. Many more cases of episodic angioedema and eosinophilia and HES must be analyzed to establish the usefulness and significance of CD69 antigen expression on PB eosinophils.

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